Exhibit C 46

Multiple Sclerosis

The Merck Manual of Diagnosis and Therapy

Section 14. Neurologic Disorders

Chapter 180. Demyelinating Diseases

Topics

[General]

Multiple Sclerosis

A slowly progressive CNS disease characterized by disseminated patches of demyelination in the brain and spinal cord, resulting in multiple and varied neurologic symptoms and signs, usually with remissions and exacerbations.

Etiology and Incidence

The cause is unknown, but an immunologic abnormality is suspected. One postulated cause is infection by a latent virus (possibly by a human herpesvirus or retrovirus), in which viral activation and expression trigger a secondary immune response. An increased family incidence and association with certain HLA allotypes suggest genetic susceptibility. Environment may be a factor: MS is more common in temperate climates (1/2000) than in the tropics (1/10,000). It has been linked to the geographic area in which a patient's first 15 yr are spent; relocation after age 15 does not alter the risk. Age at onset is typically 20 to 40 yr, and women are affected somewhat more often than men.

Pathology

Plaques of demyelination, with destruction of oligodendroglia and perivascular inflammation, are disseminated throughout the CNS, primarily in the white matter, with a predilection for the lateral and posterior columns (especially in the cervical and dorsal regions), the optic nerves, and periventricular areas. Tracts in the midbrain, pons, and cerebellum are also affected as is gray matter in the cerebrum and spinal cord. Cell bodies and axons are usually preserved, especially in recent lesions. Later, axons may be destroyed, especially in the long tracts, and a fibrous gliosis makes the tracts appear sclerotic. Recent and old lesions may coexist. Chemical changes in lipid and protein constituents of myelin occur in and around the plaques.

Symptoms and Signs

The disease is characterized by various symptoms and signs of CNS dysfunction, with remissions and recurring exacerbations. The most common presenting symptoms are paresthesias in one or more extremities, in the trunk, or on one side of the face; weakness or clumsiness of a leg or hand; or visual disturbances, eg, partial blindness and pain in one eye (retrobulbar optic neuritis), dimness of vision, or scotomas. Other common early symptoms are ocular palsy resulting in double vision (diplopia), transient weakness of one or more extremities, slight stiffness or unusual fatigability of a limb, minor gait disturbances, difficulty with bladder control, vertigo, and mild emotional disturbances; all indicate

scattered CNS involvement and often occur months or years before the disease is recognized. Excess heat (eg, warm weather, a hot bath, a fever) may accentuate symptoms and signs.

Mental: Apathy, lack of judgment, or inattention may occur. Emotional lability is commoi and may suggest an incorrect initial impression of hysteria. Euphoria occurs in some patients; a reactive depression, in others. Sudden weeping or forced laughter (concomitants of pseudobulbar palsy) indicates that corticobulbar pathways of emotional control are affected. Convulsive seizures seldom occur. Severe changes (eg, mania, dementia) can occur late in the disease. Scanning speech (slow enunciation with a tendency to hesitate at the beginning of a word or syllable) is common in advanced disease. Aphasia is rare.

Cranial nerves: In addition to optic neuritis, one or more of the following ocular signs usually occur at some time: partial optic nerve atrophy with temporal pallor, changes in visual fields (central scotoma or general narrowing of the fields), or transient ophthalmoplegia with diplopia (due to involvement of the brain stem tracts connecting the 3rd, 4th, and 6th nerve nuclei). In optic neuritis, papilledema accompanied by impaired vision can occur, and the affected pupil does not constrict as completely in response to applied light as does the other pupil; however, other pupillary changes, Argyll Robertson pupils, and total blindness are rare. Nystagmus, a common finding, may be due to cerebellar or vestibular nucleus damage. Other evidence of cranial nerve involvement is uncommon and, when present, is usually due to brain stem injury in the area of the cranial nerve nuclei. Deafness is rare, but vertigo is not. Unilateral facial numbness or pain (resembling trigeminal neuralgia) occurs occasionally, as does hemifacial palsy or spasm.

Motor: Deep reflexes (eg, knee and ankle jerks) are generally increased; Babinski's sign and clonus are often present. Superficial reflexes, particularly upper and lower abdominal, are diminished or absent. Often, the patient complains of unilateral symptoms, but examination elicits signs of bilateral corticospinal tract involvement. Intention tremor due to cerebellar lesions is common, and continued purposeful effort accentuates it. The motior is ataxic: shaky, irregular, tremulous, and ineffective. Static tremor may occur; it is especially obvious when the head is unsupported. Muscular weakness and spasticity from corticospinal damage produce a stiff, imbalanced gait; later, a combination of spasticity an cerebellar ataxia may become totally disabling. Cerebral lesions may result in hemiplegia, sometimes the presenting symptom. Painful flexor spasms in response to sensory stimuli (eg, bedclothes) may occur in late stages.

One pattern of disease includes acute optic neuritis, sometimes bilateral, with demyelination of the cervical or thoracic spinal cord (optic neuromyelitis), producing visua loss and paraparesis. Charcot's triad (nystagmus, intention tremor, and scanning speech) is common cerebellar manifestation in advanced disease. Mild dysarthria may result from cerebellar damage, disturbance of cortical control, or injury to the bulbar nuclei.

Sensory: Complete loss of any form of cutaneous sensation is rare, but paresthesias, numbness, and blunting of sensation (eg, reduced pain or temperature sense, disturbances c vibratory or position sense) may occur and are often localized, eg, to the hands or legs. Objective changes are fleeting and are often elicited only with thorough testing. A range of painful sensory disturbances (eg, burning, electrical, or paroxysmal pain) can occur, especially with spinal cord demyelination.

Autonomic: Urinary urgency or hesitancy, partial retention of urine, or slight incontinence and constipation are common when the spinal cord is affected, as are erectile dysfunction in men and genital anesthesia in women. Urinary and fecal incontinence may occur in advanced disease.

Course

The course is highly varied, unpredictable, and, in most patients, remittent. Life span is probably not shortened except in the most severe cases. At first, months or years of remission may separate episodes, especially when the disease begins with retrobulbar optic neuritis. Remissions can last > 10 yr. However, some patients have frequent attacks and are rapidly incapacitated; for a few, particularly for male patients with onset in middle age, the course can be rapidly progressive. Exposure to excess heat from fever or the environment sometimes worsens symptoms.

Diagnosis

Diagnosis is indirect, by deduction from clinical and laboratory features. Typical cases can usually be diagnosed confidently on clinical grounds. The diagnosis can be suspected after a first attack. Later, a history of remissions and exacerbations and clinical evidence of CNS lesions disseminated in more than one area are highly suggestive. Other possibilities must be considered (see Table 180-1).

MRI, the most sensitive diagnostic imaging technique, may show plaques. It may also detect treatable nondemyelinating lesions at the junction of the spinal cord and medulla (eg subarachnoid cyst, foramen magnum tumors) that occasionally cause a variable and fluctuating spectrum of motor and sensory symptoms, mimicking MS. Gadolinium-contras enhancement can distinguish areas of active inflammation from older brain plaques. MS lesions may also be visible on contrast-enhanced CT scans; sensitivity may be increased by giving twice the iodine dose and delaying scanning (double-dose delayed CT scan).

CSF is abnormal in the majority of patients. IgG may be > 13%, and lymphocytes and protein content may be slightly increased, but these findings are not pathognomonic. Oligoclonal bands, which indicate IgG synthesis within the blood-brain barrier, may be detected by agarose electrophoresis of CSF in up to 90% of patients with MS, but absence of these bands does not rule out MS. IgG levels correlate with disease severity. Myelin basic protein may be elevated during active demyelination.

Evoked potentials (see Neurologic Diagnostic Procedures in Ch. 165) are recorded electrical responses to stimulation of a sensory system. Pattern-shift visual, brain stem auditory, and somatosensory evoked potentials may be abnormally delayed early in the disease, because demyelination slows the conduction of electrical impulses in these sensory pathways.

Treatment

Spontaneous remissions and fluctuating symptoms make treatments difficult to evaluate. Corticosteroids (oral prednisone 60 to 100 mg/day tapered over 2 to 3 wk or IV methylprednisolone 500 to 1000 mg/day for 3 to 5 days) are the main form of therapy. The may shorten the symptomatic period during attacks, although they may not affect eventual

long-term disability. Patients presenting with acute severe optic neuritis may delay the onset of MS by using high-dose IV corticosteroids. Long-term corticosteroid treatment is rarely justified and can cause numerous medical complications including osteoporosis, ulcers, and diabetes. Alternatively, ACTH 40 to 80 U/day IM for 5 days tapered over 2 to 3 wk is sometimes also used.

Immunomodulatory therapy with interferon-β reduces the frequency of relapses in MS and may help delay eventual disability. Glatiramer acetate may have similar benefits for early, mild MS. IV gamma globulins given monthly may help control relapsing MS refractory to conventional therapies. Immunosuppressive drugs (methotrexate, azathioprine, cyclophosphamide, cladribine) for more severe progressive forms are not uniformly beneficial and have significant toxic risks.

Symptomatic therapies may help alleviate spasticity, fatigue, bladder dysfunction, and uncomfortable sensory symptoms. Regular exercise (eg, stationary biking, treadmill, swimming, stretching exercises) is recommended, even for patients with more advanced disease, because it conditions the heart and muscles, reduces spasticity, and has psychologi benefits. Drugs for spasticity (baclofen 10 to 20 mg po tid to qid, tizanidine 4 to 8 mg po tid) can be initiated at a low dose and cautiously increased until the patient responds. Physical therapy for gait training and range-of-motion exercises for weak, spastic limbs helps. Multiple drugs, including amitriptyline 25 to 75 mg po at bedtime, carbamazepine 200 mg po tid, and narcotic analgesics, may be required for painful sensory symptoms. The patient should maintain as normal and active a life as possible but should avoid overwork, fatigue, and exposure to excess heat. There are no good data regarding risk of vaccination.

In debilitated patients, pressure ulcers and urinary tract infections should be prevented, and the need for intermittent urinary self-catheterization must be carefully evaluated. Encouragement and reassurance are essential; clinical depression must be treated with counseling and antidepressants.